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THE WELLCOME

PHYSIOLOGICAL RESEARCH LABORATORIES

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THE WELLCOME

PHYSIOLOGICAL RESEARCH LABORATORIES

FOUNDED 1894

WALTER DOWSON, M.A., M.D., *Director*

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BROCKWELL HALL,
HERNE HILL,
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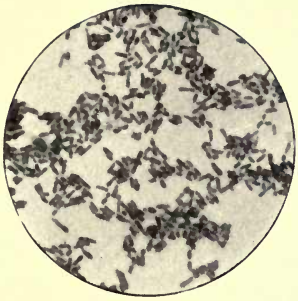
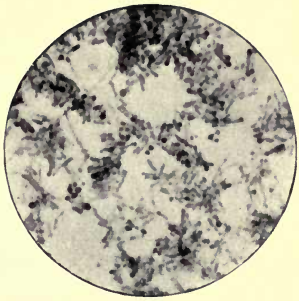
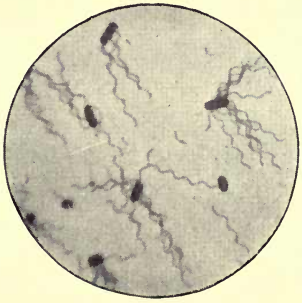


B. Diphtheriæ.



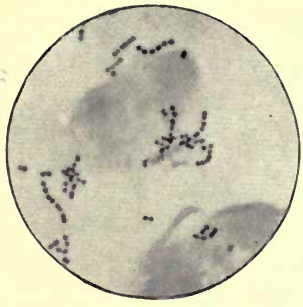
B. Diphtheriæ.



B. Typhosus.

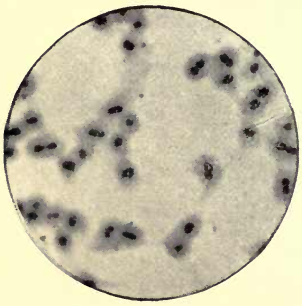
B. Tetani

B. Tuberculosis.

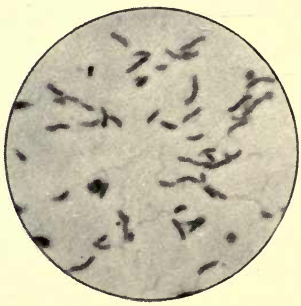


Streptococcus pyogenes

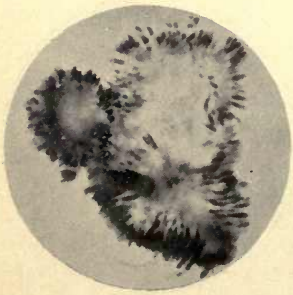
B. Anthracis.



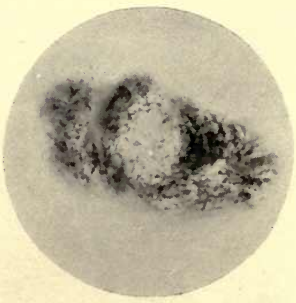
Diplococcus pneumoniæ.



Spirillum Choleræ Asiaticæ



Actinomyces.



B. Lepræ.

THE WELLCOME
PHYSIOLOGICAL RESEARCH LABORATORIES.

INTRODUCTION.

IT is now widely recognised that physiological science at the present day owes its motive and chief interest to the progress and outcome of the work bearing on cell metabolism during the last decade. The enormous international literature which, in this short time, has grown round the results achieved by one of the most brilliant groups of workers of the nineteenth century, in the domains of chemistry, physiology, and bacteriology, records so many demonstrated facts of fundamental importance, and raises suggestions of such far-reaching significance, that no little difficulty is encountered in attempting to gain a comprehensive insight into the present position.

Prominent amongst these results, and, perhaps, the most important of them all, is the fact that we are to-day in possession of a satisfactory working theory of the nature of infective disease, and of the factors involved in natural resistance and acquired immunity. The absence of such a theory may reasonably be held to have been the cause of that strange arrest of progress in natural knowledge of this subject for so many years after the very complete and suggestive work of Jenner. The first real impulse came from Pasteur, the intellectual descendant of Jenner; and from the time that Pasteur enunciated his views upon fermentation, followed as this was by the work of our own illustrious Lister, advance has been steady and sure. And although the application of principles, so fully worked out by Jenner, to the investigation of other diseases by means of animal experiment, was rapidly fruitful of the most important results, the various and contradictory theories of immunity held by different authorities served mostly to bring into relief the difficulties which surround the subject. Metchnikoff's observations on the bactericidal action of the white cells of the blood, as embodied in his famous phagocyte theory, were soon recognised as dealing with the main issue, but his generalisation was considered to be too narrow to cover all the facts when Behring's serum work was announced. The discovery by the latter that the serum of animals immunised against diphtheria contained a specific antitoxin which, when injected into other animals, could protect them

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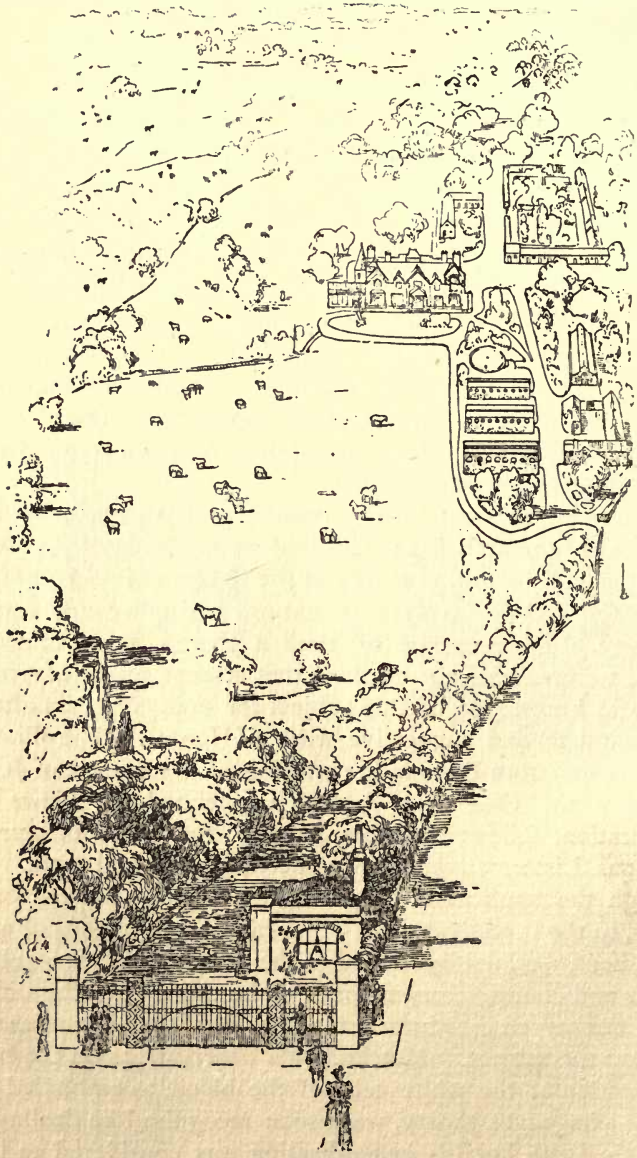


BIRD'S-EYE VIEW
OF THE
WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES AND GROUNDS.

against diphtheria toxin, was a most important step in advance. Equally important was Pfeiffer's observation that cholera vibrios introduced into the peritoneal cavity of immune animals undergo disintegration. It led Metchnikoff, using immune serum together with a small quantity of normal peritoneal exudate, to show that this phenomenon took place *in vitro* outside the animal body ; and later on Bordet demonstrated that immune serum alone, if perfectly fresh, also induces bacteriolysis *in vitro*. The latter observer further showed that, if the immune serum had lost its activity, this could be renewed by a small quantity of normal serum.

The problem thus gradually came within range of accurate investigation, and, great as the difficulties were, they gradually yielded to experiments made from this new standpoint. Investigations carried out with the object of throwing light upon the origin of the various protective substances which undoubtedly exist in the blood, appear to point to the white corpuscles as being very largely concerned in this ; and so Metchnikoff's earlier work appears in a new light which shows his original theory to be nearer the truth than was at first accepted. There are indications that antitoxins bear an intimate relation to the products of normal cell activity ; and there are reasons for thinking that the affinity between a toxin molecule and a molecule of cell protoplasm is a chemical one strictly comparable to that involved in the process by which food stuffs are assimilated. In accordance with this theory, antitoxin formation is " a process analogous to those constituting an essential portion of the normal metabolism of the organism." If anything were wanting to add to the interest and importance of this view, we should find it in this : that one of its fundamental conceptions lays down the specific character of an antitoxin as a necessary pre-condition and cause of the toxic action of the body which induces its production. It may truly be said that to-day the world stands in debt to the well balanced imagination, the carefully planned experiments, and the rigorous logic of Ehrlich for a luminous theory, the ultimate outcome of which bids fair to lead us far towards the conclusion of the whole matter.

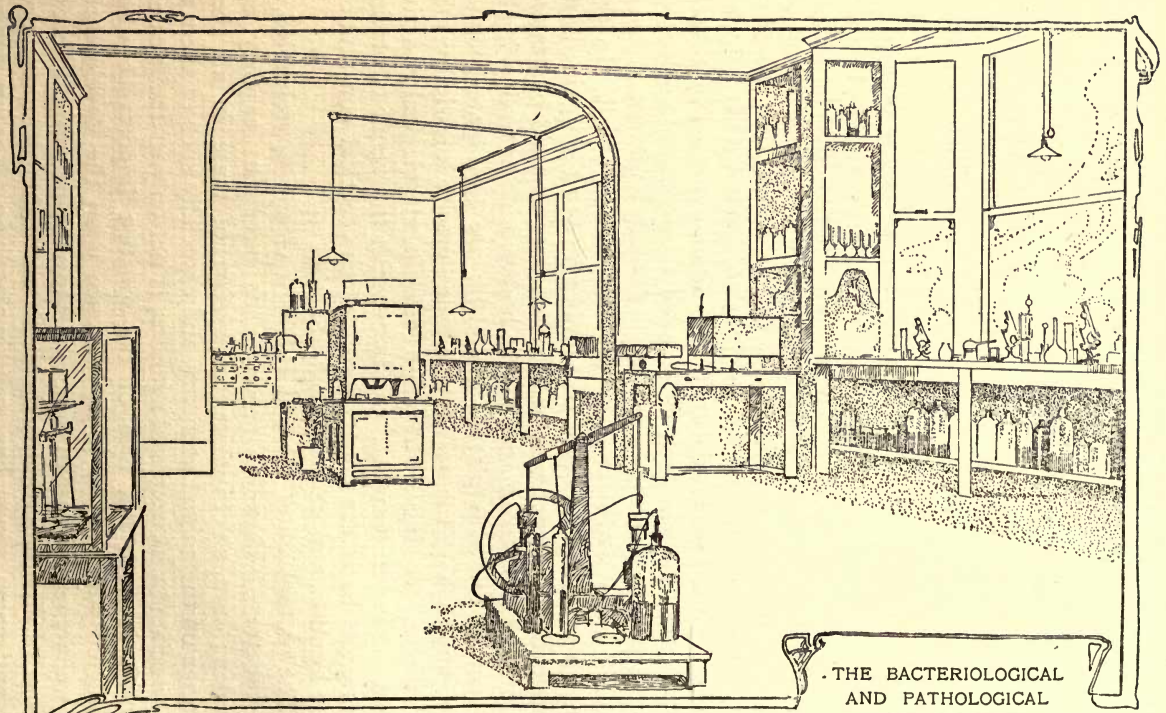
The path to this knowledge has been marked, and its successful pursuit has been largely maintained, by a commensurate increase in our knowledge of the composition and chemistry of the blood. The work of the past few years on hæmolysines and bacteriolysines presents the blood in the light of a fluid

The Wellcome Physiological Research Laboratories,
BROCKWELL HALL.

exceedingly complex in composition and capable of great variation in animals of the same species under different conditions of health and disease. The same researches have demonstrated the prominence of the part played by a large number of enzymes, until lately scarcely suspected to exist, in normal as well as in pathological cell processes; and, though the list of hæmolysines and such analogous bodies as agglutinines, bacteriolysines, enzymes, antienzymes, is already long, it seems probable that blood serum is loaded with similar bodies, of which, at present, practically nothing is known.

The genesis of these substances in the various organs and tissues of the body, and their interaction with the various products of cell metabolism and with each other, have still to be worked out; but sufficient progress has been made to warrant the conviction that the therapeutics of the future will deal more and more with substances derived from the animal body. It is highly unlikely that the successful treatment of myxœdema by thyroid substance will remain long unattended by the useful application of other products of the same class. Already suprarenal extract is finding employment, with results which promise well. In this connection it may be noted that an insight has been gained into the essential difference between the action of alkaloid bodies and that of highly complex proteid-like bodies, such as toxins, in the presence of cell protoplasm; and there are legitimate grounds for hoping that, in the near future, some precise knowledge may be gathered of the distribution of pharmacologically active substances in the tissues of the body, with the result of placing on an exact basis the connection between chemical constitution, tissue location, and pharmacological action.

The protoplasm of the cell, it is now clearly apprehended, is the theatre of chemical processes as numerous as they are complex; and an intimate knowledge of these in all their bearings on the animal economy, and especially such of them as are associated with external agencies, is not only of the greatest scientific interest, but also of the greatest importance when considered with respect to its influence upon the development and welfare of the human race. Already the beneficial effect of the use of diphtheria antitoxin needs no further demonstration, and antivenom serum has saved many lives. Nor are indications wanting that continued research in the same field will, in time, yield active remedies of a similar character for enteric fever, erysipelas, pneumonia, and other kindred diseases.



Wellcome Physiological Research Laboratories

THE BACTERIOLOGICAL AND PATHOLOGICAL LABORATORIES.

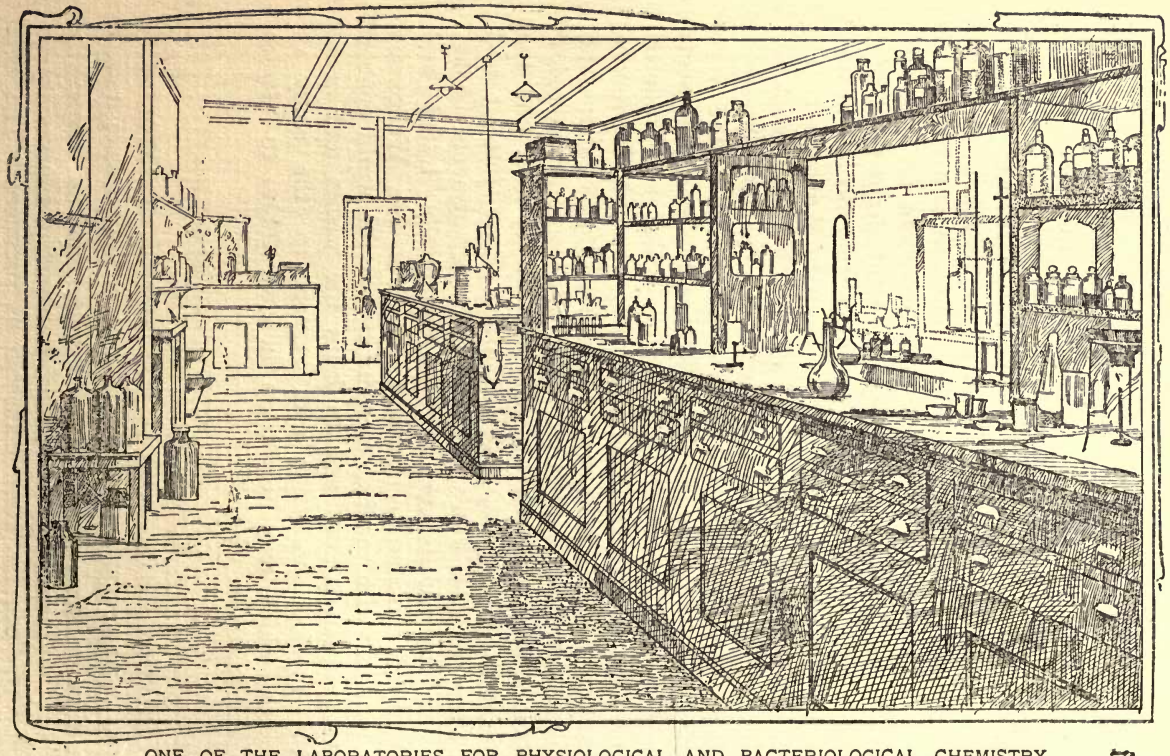
It was for the purpose of participating in the inevitable advances of scientific thought and discovery, which concern not merely institutions and individual scientific workers, but upon which the progress and intellectual status of mankind so largely depend, that the WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES were founded.

As it was recognized that the accomplishment of this purpose would involve the expenditure of very large sums of money without prospect of pecuniary return, it is evident that the motives which led to this decision were not prompted by monetary considerations. It was rather in the desire to at least keep pace with workers in other countries, that Mr. Wellcome, who is the Principal of the firm of Burroughs Wellcome & Co., established these laboratories as an institution entirely separate and distinct from his business, and under independent direction. He does not wish to disguise the fact that much of the work conducted in the laboratories has reference to the requirements of his firm. For example, the serums which are produced are supplied to the medical profession through Burroughs Wellcome & Co. Also some of the original investigations and researches which are carried out in the Wellcome Physiological Research Laboratories have special relation to new, and the improvement of known, products which have interest and importance for the firm's manufacturing departments. Likewise, various substances are physiologically tested and standardised. Naturally, through his firm, Mr. Wellcome's intimate touch with medical men throughout the world enables him to gain suggestions and to learn the wishes and needs of the medical profession with respect to the study of substances which may help them in their efforts to "lessen pain and postpone death."

DESCRIPTION OF THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES.

The New Laboratories.

The original laboratories, established in 1894, were enlarged from time to time to meet the requirements of constantly increasing work, until it was found necessary to acquire more commodious premises. The new laboratories were established at Brockwell Hall, Herne Hill, London, S.E., in the early part of 1899. As there are many medical and other scientific men who are interested in the work of these laboratories, but who are unable to avail



ONE OF THE LABORATORIES FOR PHYSIOLOGICAL AND BACTERIOLOGICAL CHEMISTRY.

Wellcome Physiological Research Laboratories.

themselves of the opportunity of personally inspecting them, a brief description of their equipment may prove of interest.

Brockwell Hall is an old fashioned country mansion, standing in its own grounds. The adaptation of these premises to the requirements of research work has been carried out with the greatest care, and no pains or expense have been spared in rendering their appointments as complete as possible.

Two of the principal laboratories are situated on either side of the entrance hall and lobby. One of these (illustrated on page 8) is the special laboratory of the Director,

Bacteriological Laboratory.

Dr. Walter Dowson, where the examination of specimens of blood, sputum, throat exudates, etc., is carried out under his personal supervision. The Director also controls the determination of the antitoxic strength of the serums issued from the establishment, and superintends the research work which is conducted as one of the chief aims of the Institution. The other laboratory (illustrated

Chemical Laboratory.

on page 10) is devoted to research work in physiological and bacteriological chemistry. Investigations are conducted here for the purpose of isolating and determining the character and composition of the active principles of glands and other animal tissues, animal and vegetable ferments, toxins, antitoxins, and similar bodies.

Another laboratory (illustrated on page 14) is devoted to the preparation and sterilisation of nutritive media

Nutritive Media.

and other materials required in bacteriological work. The Secretary's office and a dark room for photo-micrographic work are also on the ground floor of this building.

Two large dry cellars in the basement of the house have been utilised for the incubating chambers, one of which is illustrated on page 18. Here cultures of various

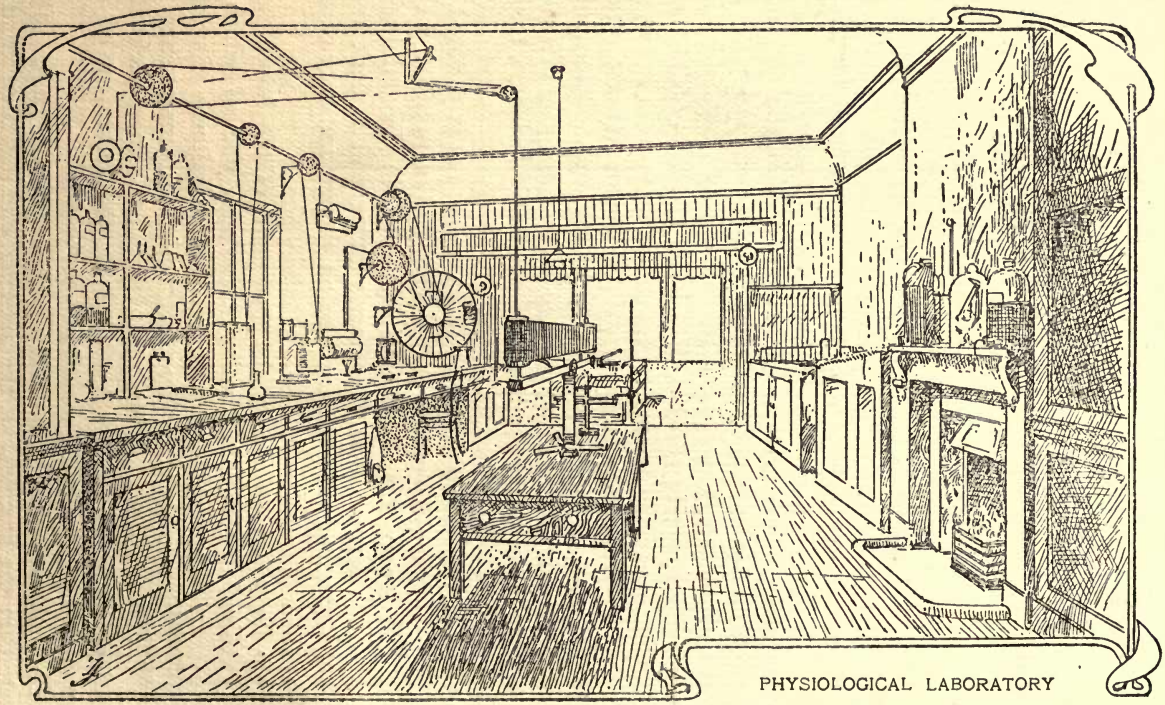
Incubating Chambers.

microbes, chiefly diphtheria, are maintained in vessels containing nutrient broth ; these yield after filtration the toxin which is needed for the treatment of the large number of animals housed in the stables.

The physiological laboratory (illustrated on page 12) is situated on the first floor of the building, and has been fitted up with great care and completeness. It contains a

Physiological Laboratory.

large kymograph by Palmer, an electric clock for automatically recording various intervals of time, a drum for taking small tracings, an operating table, fitted



Wellcome Physiological Research Laboratories

with hot water tank, Dr. Cowl's universal "holder" for small and medium sized animals, a pump for artificial respiration; in fact, all the latest and best apparatus for physiological research and for testing and standardising various drugs and chemicals. An electric motor supplies the power required. The benches, drawers, and specimen cabinet are carried out in teak.

The Library, well supplied with English and foreign standard technical works and physiological literature, is also on this floor.

On the same floor several laboratories and rooms are set apart for the manipulation of serums. When required, one of these rooms can be supplied with clean air of the desired temperature, freedom from suspended particles being effected by passage through a battery of sterilised cotton-wool filters. The necessary force is supplied by an electric motor fan. The benches, apparatus, etc., in this room are not fixed to the floor or walls, but are readily movable, so that all corners are accessible, and perfect cleanliness can be easily maintained.

Sterile Room.

Separated from this room by a carefully constructed lobby with double doors, is a general laboratory, where the phials in which the serums are issued to the medical profession are washed and plugged ready for sterilisation by heat, and then stored in tiers of trays. The hot-air steriliser and the autoclave stand on a bench fitted with a slate top.

All toxins used in the laboratories and at the stables are filtered in a separate room through a paper filter devised by the Director. The pores of this filter are blocked to the required degree by fine kieselguhr dust with the result that the clogging which is commonly experienced with other appliances for this purpose does not occur. The filtering medium, moreover, is quickly renewable for each operation. The freedom of the filtrate from microbes is ascertained by microscopic and culture tests.

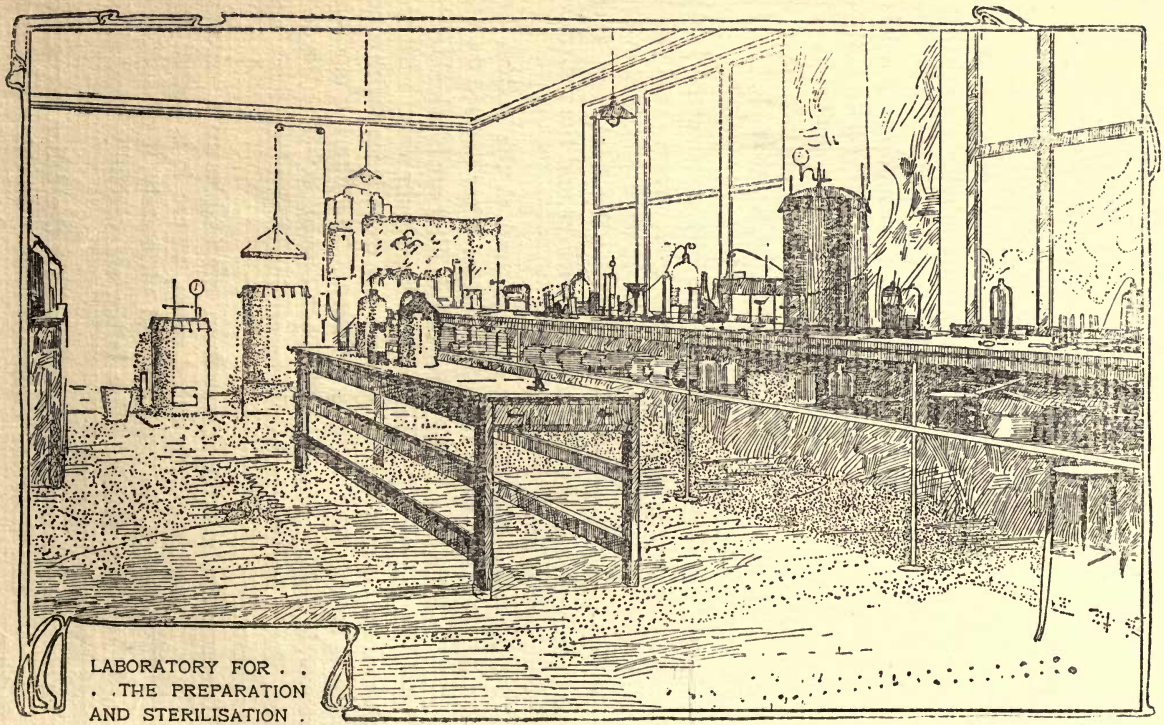
Toxin Room.

All serum is brought direct from the stables to a separate and specially fitted room, where it is stored and tested for sterility, and ultimately, if of sufficient strength, run into phials. The latter are carefully treated for sterility before being used.

Phial Room.

The packing rooms, store rooms, and the other rooms on this floor are equipped with everything necessary for the manipulation and packing of the serums, and for all the other work appertaining to the various departments of the institution.

Packing.



LABORATORY FOR . .
. .THE PREPARATION
AND STERILISATION .
OF NUTRIENT MEDIA.

Wellcome Physiological Research Laboratories.

Throughout the laboratories and the subsidiary departments the fixtures have been specially designed for their particular uses. The fume chambers, autoclaves, sterilisers, balances, vacuum pumps, electric heating apparatus, etc., are all of the most approved and modern construction. The walls and ceilings are enamelled; the floors, where not of cement, are covered with linoleum, the junction of the floor with the walls being rendered impervious to dust and moisture by means of carefully adjusted triangular fillets. The tables and benches are either of glass or slate, or are covered with lead or linoleum.

The Stables and other Adjuncts.

The new stables are situated about one hundred yards from the laboratories. They are lofty, well lighted and well ventilated, and are fitted with every convenience and contrivance conducive to the well-being of the horses. The walls are of white glazed brick and cement, the floor being paved throughout with the best stable bricks.

The old stables and coach houses of the Hall have been remodelled in accord with modern views. Near by is a special laboratory for the collection and separation of serums. This laboratory, like the stables, has been so built as to permit of the whole room being flushed with water, so that serums can be manipulated under the conditions necessary for ensuring perfect cleanliness.

Collection of Serum.

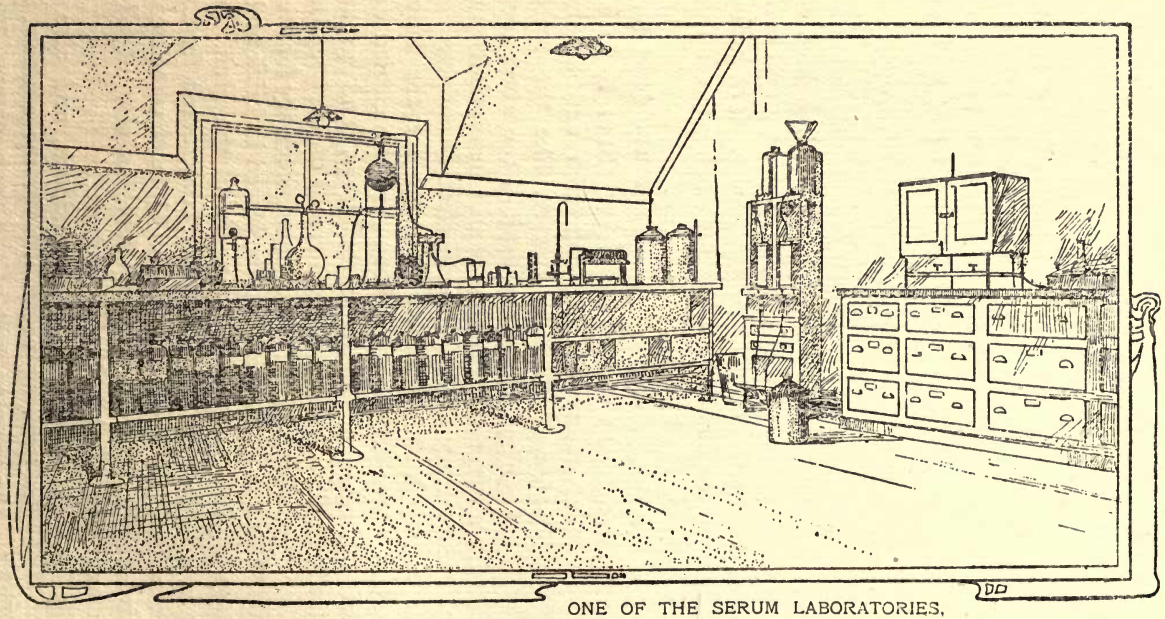
An entirely new system of drainage for the laboratories, stables and other premises has been carefully carried out.

The laboratories, stables, outbuildings, and grounds are electrically lit, the current being generated on the premises. The boiler, engine, and dynamo necessary for the generation of the current are placed in brick and cement buildings adjoining the south-west side of the Hall. Near the boiler is a large cylindrical steriliser, constructed for a working pressure of 30 lbs. The sterilisation of all large vessels containing nutritive media, etc., is effected here, as also of all vessels which have been used in the laboratories.

Electric Light.

The grounds contain a large paddock, and also gardens for growing vegetables for the animals. During the greater part of the year many of the guinea pigs, by a simple but effective arrangement, are enabled to spend most of the time in the paddock.

Paddock. Gardens.



ONE OF THE SERUM LABORATORIES.

Wellcome Physiological Research Laboratories.

The Animal House.

A large animal house is being erected, which, when completed, will accommodate all the animals required for the work of the laboratories. It will contain specially designed metabolism cages, and full provision will be made for the efficient isolation of animals inoculated with living cultures. The heating and ventilation of this building have been very carefully thought out, with a view to the health and comfort of the animals.

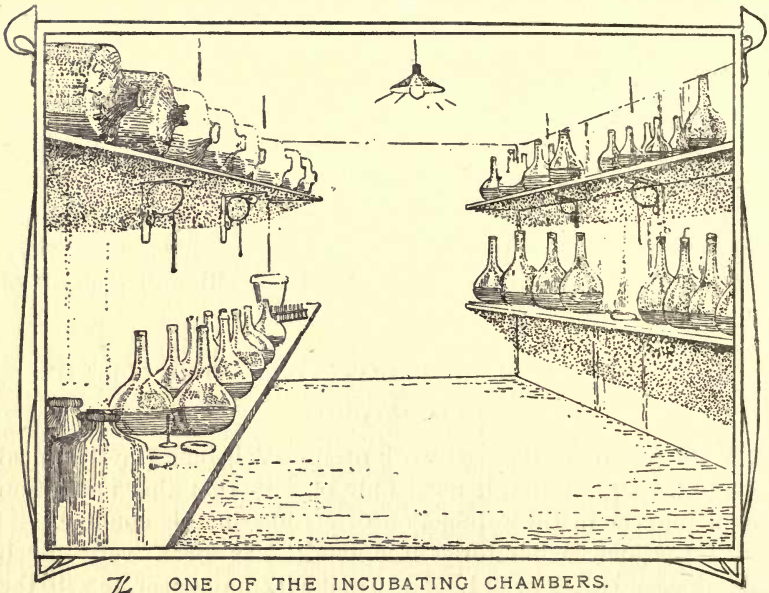
Past, Present and Prospective Work of the Laboratories.

With regard to the past work of the Wellcome Physiological Research Laboratories, it need only be said that this institution was a pioneer in the production of serums in this country.

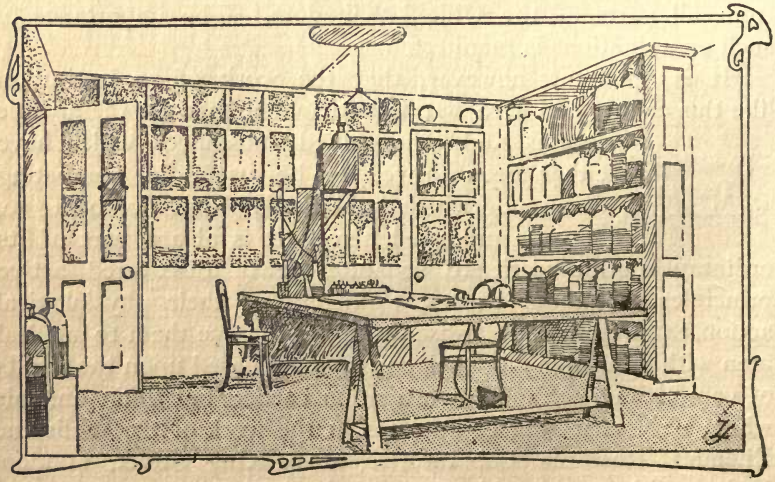
In the new laboratories the work has been very much extended, and it has been hoped to make it commensurate with the exceptional facilities which have been there provided for research and investigation in the several branches of physiological science. As examples of the varied character of the work conducted in these laboratories at the present time, reference has already been made to bacteriology, to the production and investigation of serums, and to the examination of specimens of blood, sputum, throat exudates, etc., which are sent by medical men from all parts of the United Kingdom. The importance of such examinations is manifest.

It is apparent, however, that the work of an institution like this cannot end here. It is anticipated that all therapeutic serums and other allied substances which have either been proved to be useful in combating disease or which hold out a promise of being so, may be produced here. It is also a part of its ordinary routine work to separate newly discovered active principles of animal tissues, to determine their physiological action, to carefully standardise them, and to issue them to medical men with indications for their employment based upon the results of careful and accurate investigation carried out upon animals where necessary. It co-operates in the work of the Wellcome Chemical Research Laboratories, at 6, King Street, London, E.C. Without this aid many of the investigations conducted in the latter laboratories would remain incomplete, or, perhaps

Physiological Tests and Standardisation.



ONE OF THE INCUBATING CHAMBERS.
Wellcome Physiological Research Laboratories.



ONE OF THE ROOMS IN WHICH PHIALS ARE FILLED
Wellcome Physiological Research Laboratories

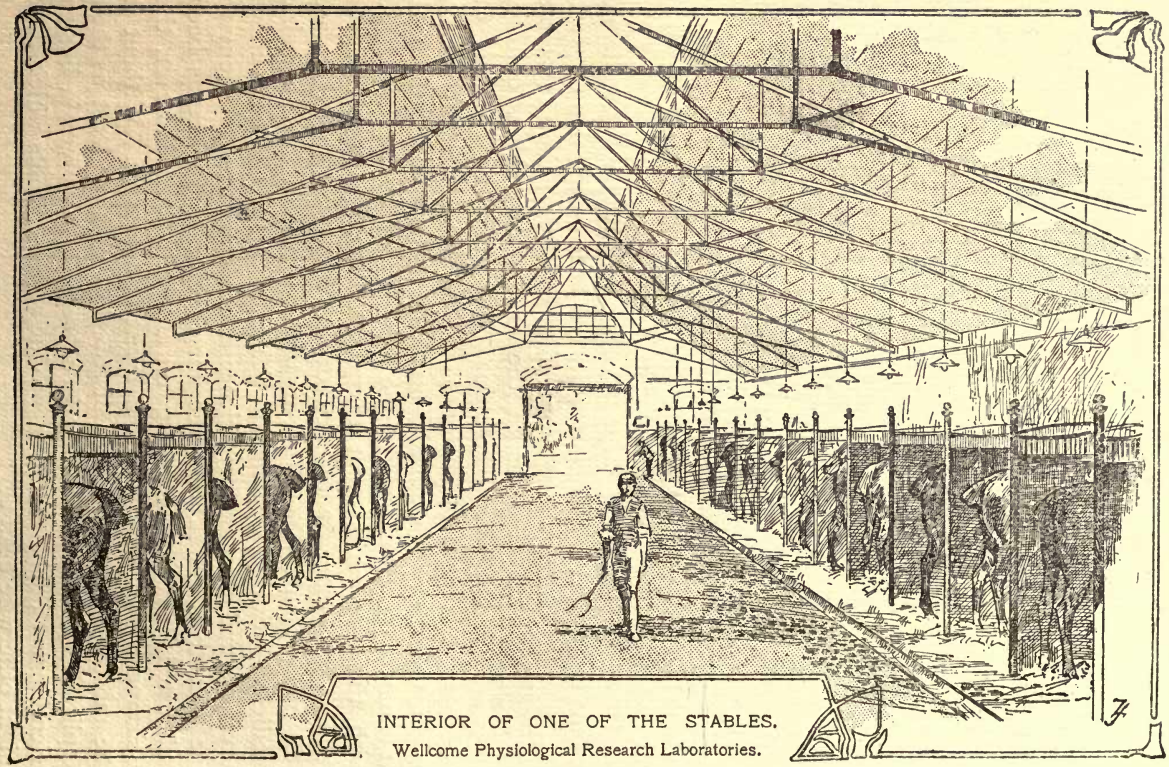
even fail to achieve the purpose for which they were primarily undertaken. In fact, in many chemical researches, particularly in those dealing with extracts from animal tissues, with principles isolated from new drugs, as well as with substances obtained by synthesis, it is absolutely necessary that physiological tests should proceed hand in hand with chemical analysis, for only in that way can the chemist be guided and his work rendered of practical value. There are many important well-known drugs, or preparations of them, notably ergot, digitalis, and strophanthus, the activity and therefore the dosage of which it is at present impossible to determine by purely chemical methods; and as these drugs are subject to variation from natural causes, independently of the treatment they may undergo in the manufacturing laboratory, it is obviously of the highest importance to the medical practitioner that he should experience no disappointment in the results obtained with them by reason of variations of strength or possibly complete inactivity. The only method of standardising such substances is by physiological tests.

Chemical Research.

If we consider the large number of invaluable medicinal agents by which our materia medica has been enriched in the past, whether obtained directly from the vegetable kingdom, as in the case of morphine, quinine, atropine, strychnine, pilocarpine or cocaine; or produced by synthetic methods in the chemist's laboratory, as in the case of chloral, antipyrine, phenacetin, sulphonal, or numerous other bodies, one cannot fail to be impressed with the possibilities that may attend future research; for it may be reasonably assumed on the one hand that there are still many plants whose investigation will reveal most valuable medicinal principles, while on the other hand the marvellous advances and triumphs of science afford abundant testimony to the fact that the skill of the chemist has by no means been exhausted. For the carrying on of such work, however, the assistance of the trained physiologist is necessary. Without it the most important chemical discoveries, so far at least as their application to the healing art is concerned, may remain barren scientific facts, debarred from producing the benefits which they might otherwise bestow.

Synthetic Products.

Such work as that carried out and contemplated in these laboratories, merits the fullest encouragement and support of the medical profession, who are most of all interested in the results.



INTERIOR OF ONE OF THE STABLES.
Wellcome Physiological Research Laboratories.

From the facts and considerations herewith presented it will be seen that these Laboratories have been established upon a broad foundation, and that no effort or expense has been spared for the attainment of the highest possible results. The constant aim has been that within their special province they should render the greatest service to the medical profession, and thus contribute to the good of humanity.

The Aim.

In this scientific spirit the Wellcome Physiological Research Laboratories have been guided from their inception, and in this spirit they will continue to be directed and controlled.

Diphtheria Antitoxic Serum, 'Wellcome.'

Since the foundation of the Wellcome Physiological Research Laboratories a number of pamphlets, leaflets and reports dealing with therapeutic serums have been issued in connection therewith.

In the early editions the origin, history and development of serum-therapy were given, as well as an explanation of the meaning of the expression "antitoxin unit." It is scarcely necessary to repeat that the antitoxin unit adopted at the Wellcome Physiological Research Laboratories is the Ehrlich-Behring unit. It is not intended in these notes to take into view any of these aspects, but merely to bring up to date, and to present in a succinct form, the progress of the treatment, and the results which have been obtained by means of it in more recent years. The only portion it is proposed to repeat is that bearing upon standardisation.

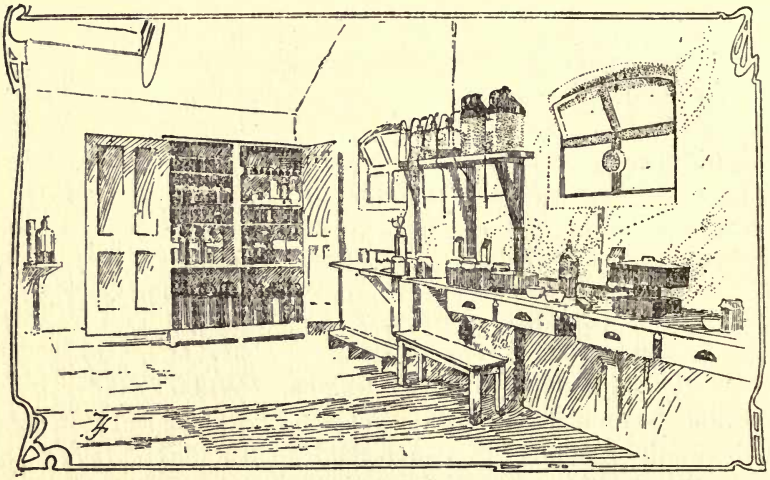
Antitoxin Unit.

Diphtheria Antitoxic Serum is standardised according to the German method as adopted and developed by Ehrlich. In its earlier form, series of guinea pigs of 250-gm. weight were injected with ten times the minimal fatal dose of a filtered broth culture (fatal in 48 hours) mixed with varying quantities of serum. The smallest quantity of the latter which would protect from all consequences, both local as well as general, formed the measure of its strength. This quantity was said to contain one tenth of a unit. Thus, if 0.01 c.c. completely protected, the serum was said to contain 10 units per c.c.

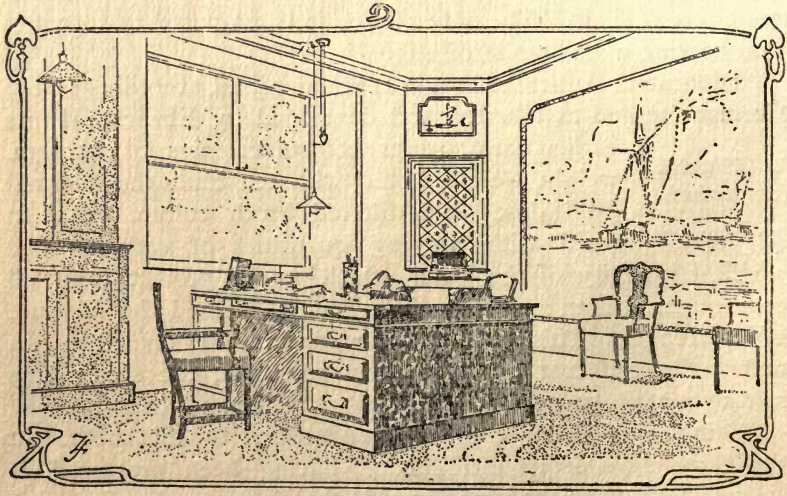
Ehrlich's Method.

Samples of serum, carefully standardised by this method in the early days of its introduction, having been preserved, it soon became known that one tenth of a unit of serum would not protect against ten times

Toxoids.



SPECIAL LABORATORY FOR THE COLLECTION OF BLOOD AND SEPARATION OF SERUMS.
Wellcome Physiological Research Laboratories.



THE SECRETARY'S OFFICE,
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the minimal fatal dose of every filtered culture. An explanation of this curious fact has been put forward by Ehrlich. The filtered culture contains, besides the specific toxin, other bodies named by him 'toxoids,' which, while incapable of causing death in moderate doses, have yet the power of combining with the antitoxin and rendering this inert. The number of minimal fatal doses which one tenth of a unit of serum will neutralise depends therefore on the ratio of toxoids to toxin in the filtrate. For the purpose of testing serum, therefore, it is necessary to use a filtrate the neutralising capacity of which has been ascertained by careful titration with standard diphtheria antitoxic serum. This standard has remained unaltered throughout, thanks to the fact that some of the earliest serum tested has been carefully preserved.

In May, 1897, a change in the method of standardising serum was introduced by Ehrlich. The presence or absence of a local swelling at the seat of injection is no longer taken as the criterion of neutralisation, but the death or survival of the animal, four days being taken as the limit; and the test dose of filtrate is no longer that which is neutralised by one tenth of a unit, but that which just suffices to kill the animal within four days when mixed with a whole unit of serum. This change does not introduce any alteration of the standard, because the test dose is ascertained by a series of experiments in which a unit of the standard serum is employed. It has the great advantage of being a purely objective method. For instance, no discrepancies can arise from difference of opinion as to what is to be considered as the smallest local swelling worthy of notice. All errors of measurement also are reduced ten per cent.

Statistics of Treatment by Diphtheria Antitoxic Serum.

Statistics.

The most valuable English statistics on the subject are those compiled by the medical officers of the Metropolitan Asylums Board; and from them may be gathered the following figures, which include all cases for the years 1894-5-6. In 1894 only a small number of cases were treated with antitoxin. In 1895, 61.8 per cent., and in 1896, 71.3 per cent., of the total cases were treated with antitoxin, it not having been employed in moribund or hopeless cases, nor in those which were doubtful in nature, or so mild as not to require any specific treatment.

The accompanying table shows clearly a regular percentage decrease in mortality *pari passu* with a regular increase in the percentage of cases treated with antitoxin.

CASES OF DIPHTHERIA TREATED IN THE HOSPITALS OF THE METROPOLITAN ASYLUMS BOARD.

Year.	Antitoxin-treated cases. Per cent. of all cases.	Mortality per cent. of all cases.
1888-93	— ..	.. 28.5
1894	— ..	.. 29.6
1895	61.8 ..	.. 22.5
1896	71.3 ..	.. 20.8
1897	80.2 ..	.. 17.5
1898	81.4 ..	.. 15.5
1899	— ..	.. 13.95
1900	— ..	.. 12.01

The Colchester Epidemic.

The Colchester epidemic in the summer of 1901 furnishes evidence of especial weight (*Journal of Hygiene*, April 1, 1902).

Up to a certain date the cases in hospital were treated with antiseptic sprays. These in all amounted to 81, of whom 21 died, giving a case mortality of 25.9 per cent. After this date all the cases were treated with antitoxin without antiseptic spray, and of 119 so treated, 7 died. The case mortality of this group was therefore 5.8 per cent.

The inference that antitoxin thus saved many lives is much strengthened by the fact that of 37 cases treated at home before the date indicated, 10.8 per cent. died, whilst of 48 cases treated at home after this date, 14.5 per cent. died. This concurrent evidence clearly shows that the severity of the disease was not declining at the time when such good results were being obtained at hospital with antitoxin.

The reader seeking further statistics may profitably refer to the following articles, wherein further convincing figures will be found :—

"Tabulation of results in Laryngeal Diphtheria."—*Medical Chronicle*, March, 1898.

"Results in London Fever Hospitals."—*British Medical Journal*, Vol. I., 1899, fol. 197, 268.

"Summary of results" by Dr. Marsden.—*British Medical Journal*, Vol. II., 1900, fol. 658.

"Conclusions formed after six years' experience with the antitoxin treatment of Diphtheria."—*Medical News*, New York, January 19th, 1901.

An exhaustive article in *The Therapist* for February 15th, 1901.

Experiments on animals have shown that the amount of antitoxin which is necessary to save life increases at a rapidly accelerating rate according to the length of time which elapses between the injection of the diphtheria virus and the administration of the curative serum, and this is amply confirmed by the results of experience in hospitals. Thus Wernicke and Behring, having determined the amount of antitoxic serum necessary to save from death a guinea pig which had immediately before been injected subcutaneously with a lethal dose of diphtheria toxin, found that ten times this amount was required to effect a cure if this administration was deferred until eight hours after the injection of the toxin; whilst twenty-four hours afterwards, fifty times the initial quantity was necessary.

[Animal] Experiment.

The Metropolitan Asylums Board states that the only limit to the administration of antitoxin is the bulk of the fluid in which it is contained. Therefore a large dose should be given at the earliest possible moment, whenever there is reason to suspect diphtheria; and in cases which progress unfavourably, the treatment may be repeated in about six hours, giving at least double the initial dose.

Limit of Dose.

Repeated Injections.

Far less, however, is to be expected from repeated injections at intervals than from one full dose given at the outset of the attack. In no case should either the administration of antitoxin or the repetition of the dose be delayed until the result of a bacteriological examination has been made known.

DOSE.

CURATIVE DOSE.—The dose for a case of moderate severity should not be less than 2,000 units, and in severe cases 4,000 units at least should be given at once. These doses should be given irrespective of age, because diphtheria is very fatal to young children. If any difference were to be made, adults would have the smaller doses, as the prognosis in diphtheria improves with the age of the patient.

Dosage irrespective of age.

As the question of the keeping quality of serums is frequently raised, it may be stated generally that, provided they are kept in a cool place at a fairly constant temperature, and protected from light, these serums may be relied upon to remain practically unaltered for at least a year from the date of issue. They are issued in phials hermetically sealed in the blowpipe flame, a method which greatly favours this result.

Keeping quality of serum.

PROPHYLACTIC DOSE.—Protective injections, of at least 1,000 units, may be administered to the rest of the family whereof one member has been attacked with diphtheria. It must be borne in mind, however, that the prophylactic action gives only a temporary protection against attack to the person so treated, the protection thus conferred lasting probably about three weeks at the most. The whole of the contents of one phial may be injected in each case. It should be carefully noted that when once a phial is opened it is highly undesirable, owing to risk of contamination, to reserve a portion of the contents for a future occasion. It should all be used on one or more patients.

Prophylaxis.

BACTERIOLOGICAL DIAGNOSIS OF DIPHTHERIA.

The injection of antitoxin at the earliest possible moment in the course of the disease may be a matter of such importance to the patient that this should be done on the clinical evidence alone where the diagnosis is doubtful; but immediate steps should be taken to confirm the diagnosis by bacteriological methods.

ON DIPHTHERIA ANTITOXIN ERUPTIONS.

In some cases the administration of diphtheria antitoxic serum is followed by rashes, transitory rise of temperature, and occasionally pains and swellings in the joints. These accidents have been shown to be also caused by normal horse serum, so that they are not in any way to be attributed to the antitoxin itself. The introduction of more highly potent serum, thus allowing a diminution of the bulk to be injected, has rendered these complications less frequent. They arise for the most part during convalescence, and do not appear to have resulted in any case in death, though they have doubtless sometimes retarded recovery.

Normal horse serum.

The following account of this subject, by Dr. Arthur Stanley, is quoted from the *British Medical Journal*, 15th February, 1902. It

deals with 500 cases of diphtheria at the North Western Hospital of the Metropolitan Asylums Board, all of which were treated with antitoxin.—"The diagnosis of doubtful cases was verified by bacteriological examination. The total number of deaths in the series was 80, a death-rate of 16 per cent. The antitoxin was injected in quantities usually of 4,000 Behring antitoxin units immediately after admission, but varied from 1,000 to 30,000 units according to the severity of the case and the time of admission after onset. No constant relation between the quantity of antitoxin given and the frequency of eruption was noted, but in one case, where antitoxins from two different sources were injected at the same time, two separate antitoxin rashes were observed; the first occurring ten days, and the second fourteen days after the giving of the antitoxins.

Different sources of antitoxin.

No special sources of antitoxin were found to cause a preponderating number of eruptions, and the eruptions occurred throughout the two years I was working with diphtheria.

"Skin eruptions appeared in about a fourth of the cases. The period of onset was usually during the second week after the giving of the antitoxin. The eruption met with was not so peculiar as to be pathognomonic, but was sufficiently marked, especially in relation to the general symptoms as to constitute a distinct type.

"There may be a little desquamation after severe and prolonged erythemata, but there is rarely any confusion between true scarlet fever occurring in the course of diphtheria and eruptions produced by antitoxin.

"The general symptoms, beyond a rise of temperature of some 3° F. and its accompanying malaise, are not marked. Pains in the joints have been frequently described but were not observed in one of these 500 cases. This result may have been due to the cases being chiefly among children. The only marked case in which pain was present was that of a girl of 13, who had frontal head-ache and lumbar pain extending down the thighs. She had a marginate erythematous eruption, and the temperature rose to 101° F.

Temperature.

"Transient early erythematous blushes, and also urticaria, often occur soon after the injection of antitoxin, but these may be generally considered to be of traumatic origin, and not to be related to any specific property of the antitoxin. The area of skin, before injection, was sterilised with soap and carbolic lotion,

and the injection syringe was boiled before each injection. No abscess at the seat of injection occurred.

"The occurrence of an antitoxin eruption during the course of a case of diphtheria did not appear to influence the prognosis seriously, though it cannot but be held that any febrile disturbance of the heart would tend to have a harmful effect. No case, however, was observed where fatal heart failure was precipitated by the occurrence of an antitoxin eruption."

Prognosis.

The Serum Diagnosis of Typhoid Fever.

A series of investigations made in different countries has gradually brought to light the fact that the serum of an animal rendered highly immune to the typhoid bacillus has a marked action upon the organisms, causing them to lose their motility, and to become collected together into little masses, which rapidly sink to the bottom of the tube containing the mixture of serum and culture.

Following this, the fact that the serum of patients suffering from typhoid fever usually gives a reaction with cultures of the typhoid bacillus, similar to though less marked than that given by the serum of animals immunised by the bacillus, has been confirmed by a host of observers. This affords fresh evidence of great weight that the bacillus typhi is really the cause of typhoid fever, and it also affords a valuable method of diagnosis.

Typhoid.

In the serum of those suffering from typhoid fever the reaction is said to have been observed as early as the fourth day. Usually it appears about the beginning of the second week, but it is undoubtedly often absent at this period. According to Courmont (*Revue de Médicine*, October, 1897), it is in cases which are exceptional, either on account of complications or severity, or because they are extremely mild, that the agglutinative power is feeble or delayed ; in simple cases of moderate severity it appears constantly about the sixth or seventh day, is active, in dilution of 1 in 100, about the tenth day, undergoes a more or less rapid rise towards the end of the febrile period (critical rise), and then disappears more or less rapidly. The persistence of the agglutinative power after recovery appears to be very variable, in some cases rapidly disappearing, in others remaining for years. The blood of those who are not suffering from typhoid fever, and from whom no history of this disease can be obtained, occasionally

gives a reaction in dilution of 1 in 10, or even 1 in 30 (the dilutions recommended by Widal). But these instances do not appear to be sufficiently numerous to seriously impair the value of the test. It is thought desirable, however, to use higher dilutions, viz., 1 in 50.

From the considerations briefly set out above it seems permissible to conclude that—(1) A negative reaction is of little value in the early days of the fever. It is of greater importance in proportion to the lateness of the period at which it is observed. It can, however, never absolutely exclude typhoid fever. (2) A positive reaction on the other hand, except with dilutions of less than 1 in 40, is sound evidence of typhoid fever present or past. The latter can be excluded if several quantitative tests have been made at different periods, and decided changes in the agglutinative power observed.

ANTI-TYPHOID VACCINE.

Anti-Typhoid Vaccine.

The question of the value of anti-typhoid vaccine as a prophylactic against enteric fever is still unanswered, the evidence which has already been collected being insufficient to enable a definite conclusion to be drawn. The statistics that have as yet appeared seem to be in its favour, but considerable doubt exists in the minds of those well able to judge, as to the benefits to be derived by means of this vaccine. When the results of the recent inoculations among the military forces in Africa have been carefully collected and tabulated we may be able to judge more accurately what amount of protection, if any, is conferred by means of the new prophylactic.

LEPROSY.

Leprosy.

It was placed on record at the Leprosy Conference, held in Berlin, October, 1897, that the treatment of leprosy up to that time had had only palliative results. It appears that this is still the position of serum-therapy as regards this disease. The epitome of current medical literature, *British Medical Journal*, January 26th, 1901, contains an important paragraph dealing with the treatment of leprosy in Norway. Many points of interest in Lie's reports on the No. 1 Leprosy Hospital, in Bergen, for the years 1895-98, are referred to. Amongst others, it is stated that three lepers were treated with Carrasquilla's serum without benefit. No further progress has been made in the serum treatment of this disease.

YELLOW FEVER.

In the *Annales de L'Institut Pasteur* No. 5, 25th May, 1898, Dr. Sanarelli gives a résumé of the results of his treatment of yellow fever by his anti-amaril serum. This serum is bactericidal, not antitoxic in action; and the author points out that, as at present prepared, it is far more useful as a prophylactic than as a curative agent. In fact, the anti-amaril serum can act effectively only when the quantity of poison already formed in the organism (the patient) does not amount to a fatal dose. He goes on to say that the ideas about this disease held by European medical men, who often compare it with cholera, and imagine that the principal lesion is a specific gastro-enteritis, are far from correct. Yellow fever really belongs to the typhus group of diseases, and often presents very serious symptoms due to the action by way of the circulation of the amaril poison upon the kidneys and nervous system.

Yellow Fever.

In all, he has treated 22 cases, of which 5 died, the mortality being thus 27 per cent. As the case mortality among the indigenous population, and those who are more or less acclimatised by residence in the country, is 50-60 per cent., and no less than 80-90 per cent. among newly-arrived Europeans, he considers these initial results, having due regard to small figures, very encouraging. The prophylactic power of the serum was tested with marked success, though on a small scale, in a prison where an epidemic of yellow fever had broken out, and was spreading in spite of isolation and disinfection. After all the prisoners and warders had been injected with the serum, not a single fresh case occurred.

ANTIVENENE.

This serum continues to maintain its claim to be a trustworthy remedy for snake-bite, if injected not later than three or four hours after the bite. A case reported in the *Lancet* of 5th January, 1901, illustrates the efficiency of fresh antivenom serum, even after the appearance of general symptoms, and in the absence of any local treatment except sucking the wound. The serum was injected into each flank, about 3½ hours after the bite.

Antivenene.

PNEUMONIA.

It should be remembered that this is a general name, and that it includes a number of instances of lung disease which are not all associated with the growth and multiplication of the same microbe in the affected tissues. Anti-

Pneumonia.

pneumococcus serum is a bactericidal, not an antitoxic agent, and might be expected to work beneficially in cases of croupous pneumonia only. The limited number of recorded cases treated with this serum do not appear to bear out the good hopes which were at first entertained of it.

TUBERCULOSIS.

Tuberculosis.

The serum treatment of phthisis has not, so far, given very encouraging results. In fact, there appears to be a fairly general agreement that the cure of this disease is still a matter mainly of hygiene and environment.

ANTI-TETANUS SERUM.

Anti-Tetanus Serum.

This serum, like anti-diphtheria serum, is antitoxic in its action. Although it may be stated that some cases of this disease have been distinctly benefited by its administration, in many others, the serum has failed. A consideration of the nature of the disease shows why this is so, and why, even more than in diphtheria, it is necessary to commence the treatment at the earliest possible moment.

Tetanus is a disease caused by the action of the toxin of the bacillus tetani upon the central nervous system; the toxin, as in the case of diphtheria, being produced in some local lesion, the seat of the growth and multiplication of the specific organisms. In tetanus, the toxin makes its way to the motor ganglion cells, partly by way of the nerves in connection with the affected part, and partly by way of the blood.

Unfortunately, the convulsive stage of tetanus is an indication not of the commencement of the disease, as is the appearance of a membrane in diphtheria, but of a comparatively advanced stage of the disease and of the occurrence of serious damage to the nervous system. The remedy should therefore be administered immediately on the manifestation of any distinct symptoms possibly tetanic, such as difficulty in opening the mouth, stiffness in the neck, or the onset, some days after the accident and without obvious cause, of an acute pain at the point of injury; and in view of the fact that the tetanus bacillus is localised and restricted to the seat of infection, attention is called to the advantage, in cases of punctured wounds, of excising freely and thoroughly the tissues around. The curative dose of anti-tetanus serum may vary from 50 c.c. to 100 c.c., in one dose or more, but, as a prophylactic in the treatment of wounds

Dose.

contaminated with dust, dirt, soil, etc., a smaller dose of 10 c.c. is said to be sufficient. This protection, however, does not persist longer than five or six weeks. It should be remembered, in considering doses, that it is impossible at present to state definitely the quantity of serum necessary to meet a given case, for so much depends on the severity of the attack and the stage at which treatment is begun. It is, therefore, better to give a large dose at the commencement. The old medicinal treatment should not be neglected.

The records of 98 cases treated by serum were collected by Weischer (*Munch. Med. Woch.*, 16th November, 1897). Of these 41 died, the mortality per cent. thus being 41.8.

The serum has been injected directly into the substance of the brain with success, and it has been claimed that this method gives the best results. A full account of this, giving details of the operation, may be found in the *British Medical Journal*, January 7th, 1899.

Anti-Streptococcus Serum.

Anti-Streptococcus Serum.

The experimental evidence (Van de Velde and others) that streptococcus erysipelatis and streptococcus pyogenes are distinct organisms, although they cannot be identified by cultural or morphological differences, is very strong, and is in some degree endorsed by clinical experience with anti-streptococcus serum. Many who have used this serum in cases of puerperal fever, erysipelas, septicæmia, and other infections presumably streptococcal, are quite satisfied that in some cases its administration has saved life; but that in other cases, to all appearances, equally suited for the treatment, it has failed to do good. Such results are quite conformable with the other evidence tending to show that there are at least several distinct varieties of pathogenic streptococci.

Septicæmia due to bacillus or diplococcus.

A point to be specially borne in mind is that all cases of puerperal fever, spreading inflammation of the skin or subcutaneous tissues, are not necessarily associated with the presence of actively growing streptococci. They may be due to some form of bacillus or diplococcus, and so would not be benefited by injections of anti-streptococcus serum. The importance of ascertaining by bacteriological tests the kind of organism at work in all such cases is thus manifest.

BACTERICIDAL SERUMS.

After, however, making all allowance for the failure of the last-mentioned serum, due to the circumstances above indicated, it has been recognised for some time past that bactericidal serums, of which anti-streptococcus serum is an example, do not work in a degree at all comparable to antitoxic serums, such as diphtheria antitoxic serum, and the difference is one not merely of degree. To some extent it is associated with the capacity of an organism to elaborate diffusible toxins which act at a distance from the more or less special and localised regions which are the seat of bacterial activity. But this is not all, for the bodies of some of these organisms, whether alive or in a state of disintegration, have poisonous effects which again may be localised or general. Nuttall's observations on the bactericidal action of serum were followed up by Buchner, who attributed it to the presence in the blood of bodies which he called alexins. Bordet's work on hæmolysis brought out the fact that there is a close similarity between this and bacteriolysis. Ehrlich's elaborate and accurate work on hæmolysis led to some definite knowledge of the nature of and of the part played by Buchner's alexins (Ehrlich's complement), and has given a great impulse to the further study of this subject.

Bactericidal Serums.

Already it is perceived that Metchnikoff's observations on the white cells of the blood must be brought into line with the serum work of the past three or four years, and a large amount of work is in progress with this end in view. It may be enough to state here that the work in one direction and another, up to the present date, is opening up a biological problem, the settlement of which necessitates research upon some fundamental observations and conceptions. A knowledge of the real nature of "immune body" and "complement," and of the seat of their production, involves a deeper knowledge of normal cell life and metabolism in every tissue of the body. It appears more than likely that some considerable time will elapse before medical men will have in their hands bactericidal serums as trustworthy in action as the diphtheria antitoxic serum.

Research of the Future.

Cancer.

There is a growing feeling that we are scarcely at the threshold of the "cancer problem," and that even more than in the case of bactericidal serums, biological questions of the first importance are involved in its solution. It may be said that the problem has not even yet taken a definite shape. Whether some of the diseases of this class are causally connected with outside infection by some specific form, which finds a field of development only in tissues previously damaged; whether the new material has its origin in some inherited peculiarity of structure, owing its capacity for growth and metastatic multiplication, to an inherited but for a time latent power, or to a stimulus derived from structural or functional alterations in another part of the body; whether the disease is communicable to a normally healthy individual by the constituent cells of such a growth, are questions which need only be stated to bring out the fact that we have in hand a problem with side issues and ramifications of even greater ultimate importance than the subject immediately before us. It will be a long and difficult work, but it is hoped that some useful section of it may be undertaken here with success sooner or later.

Cancer.

The following contribution to THE LANCET, *September 20th, 1902, by Dr. W. Vernon Shaw, one of Dr. Dowson's colleagues in the Wellcome Physiological Research Laboratories, takes into account the most recent work bearing on this problem, and deals with the whole question from a broad biological point of view.*

THE CANCER PROBLEM.

Tumours and new growths have their origin in the proliferation of tissues, the cell elements of which retain most of their morphological characteristics. All newly-formed cells arise from equivalent tissue elements. This is the fundamental fact of cellular pathology. Tumour formation is a progressive process continually diverging from the state of health. It may be asked, What is the most prominent characteristic of tumour cells as opposed to normal physiological tissue? It is that their vegetative functions dominate all other functions of the cell. Their reproductive activity overpasses that in any other direction.

Malignant tumours—*e.g.*, carcinomata—are characterised by

a cell-proliferation that, in its biological relations, enters into opposition with the physiological tissues from which they are derived. The more malignant the tumour in its clinical aspects the more does this proliferation and reproduction of the cancer cells become a prominent feature of the growth. This is especially seen in the peripheral growth and penetration of surrounding tissues. Another important feature of these tumours is that they never reach maturity ; they are never fully-developed tissues, structurally or otherwise. Degenerations are extremely common and testify to the unstable nature of the new growth.

What, then, is the biological aspect of these conditions and what is the biological position of the cells? That the life-history of cancer cells is atypical cannot be doubted when the nuclear changes in these cells are studied. Abnormal mitotic figures are extremely common. Asymmetrical division of the nucleus is frequently observed. In certain forms of sarcoma giant cells are a prominent feature. Hyperplasia of the nucleus and hyperchromatosis of certain mitotic figures are also characteristic of these new growths. These facts point to changes in the life-history of the cells. Again, in carcinomata certain bodies have been observed in constant and close relation with the nucleus of the cancer cells. Some have considered these to be parasitic organisms causally connected with the changes referred to above. Others claim that these are degenerate portions of the nucleus or some endogenous structure formed from the nucleus. Assuming this latter explanation, these bodies give a further indication of the abnormal protoplasmic activity of the cell.

How, then, do the above nuclear changes influence the life-history of the cell? To the nucleus alone is assigned the perpetuation of the type and characteristics of the cell from generation to generation, and when any alteration takes place in the nucleus there are corresponding changes in the cell. The nucleus plays an important and controlling part, not only in the process of cell-division, but in the functional activity of the cell.

Recent experiments have shown that the stimulation of the ova of certain lowly-organised animals will cause the multiplication of cells and the ultimate development of free swimming larvæ from such ova without previous fertilisation of the ova by spermatozoa. Adult organisms do not develop, but larvæ capable of independent existence can be produced. This

result has been obtained by acting upon the ova with strychnine, and also by mechanical agitation of the ova. The multiplication of cells in these larvæ is comparable with the attempts at reproduction of tissue in partially damaged structures, of which the giant cells in tubercle and the vascular connective tissue of healing wounds are examples. The growth of cancer cells is then to be looked upon as an effort of reproduction in damaged tissue, the incidence of the damage falling upon the nuclear structures. This damage alters the nature of these structures so that the vegetative functions of the cell run riot, and the cells become parasitic towards the organism in which the growth is taking place. The nature of the changes in the cancer cells and their life-history thus becomes the important point from which the origin of the cancer process must be determined.

What is the cause of this vegetative activity? Is it an initial damage to the cells in response to which there is an over-active attempt at repair? The peculiar frequency of such disease in organs once active but now undergoing involution would suggest this explanation, and also the frequent origin of malignant growths in damaged tissue further supports this view. This is in accordance with Weigert's observations on the over-production of damaged parts in the process of repair. Hence in considering the etiology of malignant growths the causation of this vegetative activity must be investigated. It may be chemical, as in the experiments with strychnine referred to above, or it may be biological, as in the theories that have been advanced as to the microbic origin of cancer. The actual epithelial cells are the source of the infective process, as shown by the reproduction of the type of cell in secondary growths, and the penetration of the surrounding tissues by the epithelial cells.

This view of the importance of the cancer cells, in a malignant growth is hardly in accord with the views of those who maintain that it is the degeneration of the surrounding tissues, particularly the connective tissue, that allows of the overgrowth of epithelial cells. But such a degeneration of the connective tissue has never been clearly demonstrated as a cause; and, in the case of most cancers, there is a considerable increase of the adjacent connective tissue. This hypothesis then draws attention to the nuclear changes in cancer cells and the consequent increase in the vegetative activity of these cells.

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